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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/483,434	01/14/2000	JEFFERY L. MILLER	14014.0360	8390

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/483,434	MILLER ET AL.
	Examiner	Art Unit
	Gerald G Leffers Jr., PhD	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,9,10 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9 and 10* is/are allowed.

6)☒ Claim(s) *3 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 6/8/2004, in which applicants presented arguments and an additional claim (claim 19). Claims 3, 9-10 and 19 are pending and under consideration in this application. This action is FINAL as the new grounds of rejection presented herein were necessitated by applicants' amendment of the claims to include new claim 19.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 3 is directed to a method for delivering a biologically active molecule into a cell comprising 1) covalently linking a molecule to the cell surface, wherein the molecule can act as a surface receptor, 2) complexing the biologically active molecule with a ligand for the surface receptor, and 3) contacting the biologically active molecule-ligand complex with the cell surface, whereby the biologically active molecule is delivered into the cell, wherein the covalently linked molecule is biotin and the ligand is avidin or streptavidin. **This rejection is maintained for reasons of record in the previous office action, mailed 3/4/2004, and which are repeated below.**

Claim 3 is rejected under 35 U.S.C. 102(b) as being anticipated by Wojda and Miller (Molecular Biology of the Cell, November 1997, Vol. 8, No. Suppl., p86A).

The contents of the meeting abstract are summarized as follows:

Endocytosis Mediated by Biotin-Avidin Crosslinking of Surface Proteins Does Not Require GPI-Proteins ((U. Wojda and J.L. Miller)) Laboratory of Chemical Biology, NIDDK, NIH, Bethesda Md 20892

Glycosylphosphatidylinositol anchored proteins (GPI-proteins) are abundant on all hematopoietic cells, and their clustering is associated with signal transduction and endocytosis. We tested the hypotheses that 1. general crosslinking of proteins on the exterior of cells leads to their endocytosis and 2. GPI-proteins are required for this process. Biotin-avidin (BA) crosslinking of the surface proteins in the absence of endocytosis was demonstrated on human red blood cells by flow cytometry and Western blotting. Endocytosis of fluorescein-labeled avidin was compared in native erythroleukemia K562 cells (GPI+) and a mutant cell line that does not express GPI proteins (GPI-). BA crosslinking did not affect K562 cells growth and viability as assessed by cell counting and dye exclusion. Fluorescent avidin was initially evenly distributed on the cell surfaces, but after 48 hours surface fluorescence was no longer detected. Internalization of the BA crosslinked surface proteins was observed within one hour and fluorescence signal was detected in the cells for six cell divisions. No internalization occurred at 4°C. No differences in the appearance of time course of BA mediated endocytosis between the GPI+ and GPI- K562 cells were noticed. In summary, BA crosslinked surface proteins on K562 cells undergo endocytosis and GPI-proteins are not required for this process.

In a telephonic interview with the examiner (1 March 2004) in response to a proposed Examiner's Amendment to cancel claim 3 and allow claims 9-10, and after having a copy of the relevant art faxed to her, applicants' representative asserted that the fluorescein molecule would not constitute a "biologically active" molecule as defined in the specification. This assertion is inaccurate. The specification teaches that a "biologically active molecule" means a molecule that, when introduced into a cell, can affect processes or reactions occurring within a cell (i.e. page 4, line 20 of the instant specification). In the Wojda and Miller Abstract, the biologically active molecule would be the fluorescein that is linked to avidin and transported into the targeted cell. After all, it is reasonable to expect that the targeted cells did not efficiently fluoresce prior

to the introduction of the fluorescein into the cells. The examiner knows of no other way in which the experiments described above could have been performed without the covalent linkage of biotin to the cell surface (i.e. the covalently linked receptor).

Response to Arguments

Applicant's arguments filed 6/8/2004 have been fully considered but they are not persuasive. The response filed on 6/8/2004 essentially argues that fluorescein is not a "biologically active molecule" as defined in the specification, even though the specification states that a biologically active biomolecule is "a molecule that, when introduced into a cell, can affect processes or reactions occurring within the cell" (page 4, line 20 of the instant specification). The crux of the response is that since fluorescing was not a process occurring in the cell prior to transfection with the avidin-avidin complex, the teachings of the Wojda & Miller abstract do not apply. Stated another way, the response essentially argues that fluorescence is a non-naturally occurring process or reaction that does not occur in the absence of the transfection step. The response directs the examiner to page 5, line 17, which further defines a biologically active molecule as one or more molecules that can, upon entering the cell, affect cellular metabolism or other cellular activities. The response further argues that fluorescence is not a cellular activity or part of cellular metabolism and that the fluorescence reaction does not affect processes or reactions occurring in the cell at all. The response points to page 5, lines 18-21, for examples of molecules that meet the limitation of being a biologically active molecule (e.g. enzymes). Further, the response argues that the specification states "The invention also provides a method for delivering marker-molecules into a cell..." and that fluorescein is cited as being a marker molecule (page 6, lines 1-2). It is argued that applicants have thus made it clear that

fluorescein and other marker molecules are considered to be distinct from "biologically active molecules" as defined in the instant specification.

Applicants' arguments are not persuasive because the assertion that there is no overlap between the marker molecules and the term "biologically active molecule" is not accurate. There is no explicit language in the definitions of the terms "biologically active molecule" and "marker molecule" that precludes an interpretation of the term "biologically active molecule" from encompassing markers such as fluorescein. The examiner is required to give limitations in the claims the broadest reasonable interpretation that is consistent with the disclosure provided by applicants. The specification teaches that a "biologically active molecule" is one that affects a process in the cell and that it can be an enzyme. There is no caveat present in the definition provided by the instant specification for a "biologically active molecule" that it affects a "natural" process within the cell or a process that was ongoing prior to transfection with the biologically active molecule. Likewise, there is no explicit statement that marker molecules that act as enzymes and which affect a cellular process (e.g. fluorescence) cannot be considered as also satisfying the limitation of being "biologically active molecules". Applicants' argument that there is an implicit exclusion of marker molecules such as fluorescein is not convincing as fluorescein meets all of the requirements for being a "biologically active molecule" and is of scientific and biological importance, for example, with regard to characterizing the mechanism of endocytosis in different cell types (e.g. as taught by Wojda and Miller). Therefore, it is reasonable to read the term "biologically active molecule" broadly as including a subset of molecules that are also encompassed by the term "marker molecules".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection, necessitated by applicants' amendment of the claims in the response filed on 6/1/2004.**

Claim 19 comprises a negative limitation that states, "wherein the biologically active molecule is not fluorescein." There is no literal support in the originally filed claims or specification for this new, negative limitation. Therefore, the negative limitation recited by claim 19 is impermissible NEW MATTER.

Conclusion

Claims 9-10 are allowed. Claims 3 and 19 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

ggl

GERRY LEFFERS
PRIMARY EXAMINER